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Term:

cisplatin with ethanol

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| | | | |
|------------|--|--------|------------|
| <u>L18</u> | L16 and micelle | 1 | <u>L18</u> |
| <u>L17</u> | L16 and l13 | 1 | <u>L17</u> |
| <u>L16</u> | cisplatin with ethanol | 28 | <u>L16</u> |
| <u>L15</u> | L13 and l8 | 2 | <u>L15</u> |
| <u>L14</u> | L13 and l8 | 2 | <u>L14</u> |
| <u>L13</u> | L12 or l5 | 1628 | <u>L13</u> |
| <u>L12</u> | DSPG | 124 | <u>L12</u> |
| <u>L11</u> | l8 and l5 | 1 | <u>L11</u> |
| <u>L10</u> | l8 same l5 | 1 | <u>L10</u> |
| <u>L9</u> | l8 with l5 | 1 | <u>L9</u> |
| <u>L8</u> | micelle with ethanol | 96 | <u>L8</u> |
| <u>L7</u> | L6 same l5 | 24 | <u>L7</u> |
| <u>L6</u> | insoluble or cisplatin | 242250 | <u>L6</u> |
| <u>L5</u> | charged lipid or phosphatidyl glycerol or DMPG | 1584 | <u>L5</u> |
| <u>L4</u> | DMPG same micelle | 5 | <u>L4</u> |
| <u>L3</u> | DMPG with micelle | 0 | <u>L3</u> |
| <u>L2</u> | micelle same phosphatidyl glycerol | 3 | <u>L2</u> |
| <u>L1</u> | micelle with phosphatidyl glycerol | 1 | <u>L1</u> |

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L2: Entry 1 of 3

File: USPT

Mar 27, 1990

DOCUMENT-IDENTIFIER: US 4911929 A

TITLE: Blood substitute comprising liposome-encapsulated hemoglobin

Detailed Description Paragraph Right (7):

As the dry lipid layer is hydrated by the hemoglobin solution, multilamellar vesicles (MLVs) form (see FIG. 6). This is because of the amphipathic nature of the individual lipids, meaning both hydrophilic and hydrophobic portions co-existing on the same molecule. On distearoyl phosphatidyl, the phosphatidylcholine head group is hydrophilic and the two stearoyl chains (18 carbon saturated fatty acids) are hydrophobic. When the hemoglobin solution is added to the homogenous film of lipids, the hydrophobic tails or stearoyl chains cling together, and pair up with stearoyl chains of other lipids to exclude water. The phosphatidylcholine head group orients towards the water (forming either a micelle (FIG. 2) or a patch of lipid bilayer (FIG. 3). The lipid bilayers form liposomes (FIG. 4) which can have a single bilayer (FIG. 5) or have multiple bilayers or lamellae on the outside but an aqueous space captured inside (FIG. 6). The use of the charged lipid, dimyristoyl phosphatidyl glycerol (DMPG) greatly aids to increase the captured aqueous volume. FIGS. 1-6 will be more fully discussed below.

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L4: Entry 3 of 5

File: USPT

Aug 1, 2000

DOCUMENT-IDENTIFIER: US 6096336 A

TITLE: Liposomal prodrugs comprising derivatives of camptothecin and methods of treating cancer using these prodrugs

Detailed Description Paragraph Right (22):

Any lipid or mixture of lipids which forms liposomes and/or micelles is suitable for use in the present invention. Phosphatidylcholines, including, for example, L-.alpha.-dimyristoylphosphatidylcholine (DMPC), L-.alpha.-dipalmitoylphosphatidylcholine (DPPC) and L-.alpha.-distearoylphosphatidylcholine (DSPC) are suitable. Also, phosphatidylglycerols, including, for example, L-.alpha.-dimyristoylphosphatidylglycerol (DMPG) are suitable. The DMPC and DMPG are both fluid phase at 37.degree. C., while DSPC is solid phase at 37.degree. C. Since the presence of negatively charged lipid in the liposome membrane causes the liposomes to repel each other, small amounts, such as, for example about 10%, of an negatively charged lipid, such as distearolphosphotidylglycerol (DSPG), may be incorporated into the DSPC liposomes. Other suitable phospholipids include: phosphatidyl-ethanolamines, phosphatidylinositols, and phosphatidic acids containing lauric, myristic, palmitic, palmitoleic, stearic, oleic, linoleic, arachidonic, behenic and lignoceric acid. Another suitable lipid includes cholesterol.

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L7: Entry 3 of 24

File: USPT

Jan 23, 2001

DOCUMENT-IDENTIFIER: US 6176842 B1

TITLE: Ultrasound assembly for use with light activated drugs

Detailed Description Paragraph Right (117):

Liposomes are typically formed spontaneously by adding water to a dry lipid film. Liposomes which include light activated drugs can include a mixture of the commonly encountered lipids dimyristoyl phosphatidyl choline ("DMPC") and egg phosphatidyl glycerol ("EPG"). The presence of DMPC is important because DMPC is the major component in the composition to form liposomes which can solubilize and encapsulate insoluble light activated drugs into a lipid bilayer. The presence of EPG is important because the negatively charged, polar head group of this lipid can prevent aggregation of the liposomes.

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L7: Entry 4 of 24

File: USPT

Dec 5, 2000

DOCUMENT-IDENTIFIER: US 6156339 A

TITLE: Process for preparing solid pharmaceutical dosage forms

Brief Summary Paragraph Right (27):

The process of the present invention allows the in-situ association of the pharmaceutically active substance with the lipid to form an association which is stable throughout the drying process as the carrier/filler network is formed. The association between the pharmaceutically active substance and the lipid may either be as a result of the partitioning of the pharmaceutically active substance into the lipid structures, by direct binding of the pharmaceutically active substance to the lipid molecules or by adsorption of the pharmaceutically active substance onto the surface of the insoluble lipid particles. Different interactions will occur depending on the physicochemical properties of the drug and of the lipid. Drugs with high lipid solubility or a high log P are likely to interact due to a partitioning effect into the lipid region. For charged drugs, an ion pair interaction can occur with oppositely charged lipid molecules or surface binding can occur with lipid particles. Suitable lipids can therefore be selected to maximise the extent of the interaction. The carrier and filler are responsible for forming the network of material which carries the dosage of the pharmaceutically active substance complexed with the lipid in the dried dosage form. Some carriers, such as gelatin also act as an emulsifying agent which enables the lipid material to be effectively dispersed.

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L7: Entry 5 of 24

File: USPT

Oct 3, 2000

DOCUMENT-IDENTIFIER: US 6126966 A

TITLE: Liposomes containing a cisplatin compound

Detailed Description Paragraph Right (66):

As described in Example 5, cisplatin-containing liposomes were prepared in accordance with the present invention from HSPC/Chol/mPEG-DSPE in a molar ratio of 50.6/44.3/5.1. A comparative liposome composition was prepared, which was identical to the liposomes of the present invention, except mPEG-DSPE was replaced with the same molar amount of distearyl phosphatidyl glycerol (DSPG), which has the same hydrocarbon tail and the same charge in the polar head group as mPEG-DSPE. The comparative liposome composition, lacking the hydrophilic polymer, did not have a surface coating of hydrophilic polymer chains on either the inner or outer lipid bilayers.

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L16: Entry 4 of 28

File: PGPB

Oct 25, 2001

DOCUMENT-IDENTIFIER: US 20010033861 A1

TITLE: Liposomes containing an entrapped compound in supersaturated solution

Detail Description Paragraph (36):

[0071] The liposomes for use in this study were prepared in the presence of ethanol during the first stages of liposome formulation and a study was performed to determine the effect of ethanol on the solubility of cisplatin. Hence, the solubility of cisplatin at 1 and 8 mg/ml at room temperature and at 65.degree. C. in 0.9% NaCl and in 20% ethanol in 0.9% NaCl was examined. At 1 mg/ml, cisplatin was soluble under all conditions, while at 8 mg/ml, most of the cisplatin precipitated at room temperature, yet was mostly soluble at 65.degree. C. Lowering the temperature back to room temperature led to the precipitation of most of the 8 mg/ml of the cisplatin, in both the absence and presence of 20% ethanol. Thus, it can be concluded that the presence of 20% ethanol did not improve the solubility of cisplatin. NMR measurements indicate that the solubility of free cisplatin in the aqueous phase is limited to .about.2 mg/ml, and is increased upon a rise in temperature to 60.degree. C. The NMR experiments show detection of a peak whose integration is proportional to .about.2 mg/ml, whereas the insoluble platinum precipitate is in fact undetected. In the case of the liposomes, nearly all the cisplatin accounted for by atomic absorption is soluble in the intraliposomal aqueous phase, which suggests that the intraliposomal concentration is higher than 2 mg/ml, which is the solubility at room temperature. It was found that in spite of the fact that the concentration of cisplatin during liposome preparation was above the solubility at room temperature (or 4.degree. C.), nearly all the cisplatin in the liposomes behaved as if soluble in the intraliposomal aqueous phase. From the solubility studies it is clear that ethanol is not responsible for the higher than expected drug-to-lipid ratio.

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L16: Entry 8 of 28

File: USPT

Oct 2, 2001

DOCUMENT-IDENTIFIER: US 6297245 B1

TITLE: Cisplatin and folic acid administered to treat breast cancer

Brief Summary Paragraph Type 1 (1):

(1) Combining cisplatin and folic acid in a solvent at a molar ratio of about 1:0.05 to 1:1 so that the percentage of cisplatin is 0.005% to 0.25% in the aliquot, whereas said solvent is water containing suitable amount of sodium bicarbonate, 0.1% to 99% methanol in water, 0.1% to 99% ethanol in water, 0.1% to 99% acetone in water, 0.05% to 5.0% sodium chloride in water, 0.0001 N to 1.0 N hydrochloric acid, or a mixture of said solvents.

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L16: Entry 13 of 28

File: USPT

Dec 14, 1999

DOCUMENT-IDENTIFIER: US 6001817 A

TITLE: Pharmaceutical composition comprised of cisplatin, and processes for making and using same

Brief Summary Paragraph Type 1 (1):

(1) Weigh a suitable amount of cisplatin and a suitable amount of the special carrier, according to the previous paragraph, in a suitable solvent so that the percentage of cisplatin is 0.005% to 0.25% in the aliquot, whereas said suitable solvent is water, methanol, ethanol, acetone, 0.1% to 99% methanol in water, 0.1% to 99% ethanol in water, 0.1% to 99% acetone in water, 0.05% to 5.0% sodium chloride in water, 0.0001 N to 1.0 N hydrochloric acid, or the mixture of said solvents.

Brief Summary Paragraph Type 1 (5):

(5) Optionally, the dried composition from step (4) is reconstituted to a solution or a suspension by a suitable solvent so that the percentage of cisplatin is 0.005% to 0.25%, preferably 0.01% to 0.1%, whereas said suitable solvent comprises water, ethanol, 0.1% to 90% ethanol in water, 0.05% to 5.0% sodium chloride in water, 0.0001 N to 1.0 N hydrochloric acid, or the mixture of said solvents.

CLAIMS:

1. A method of preparing a pharmaceutical composition which comprises a cisplatin complex comprising (i) cisplatin and (ii) a special carrier comprising adenosine, guanosine, cytidine, uridine, deoxyadenosine, deoxyguanosine, deoxycytidine, or thymidine, or mixtures thereof; and at least one excipient; wherein said pharmaceutical composition has a molar ratio between said cisplatin complex and said special carrier in the range of 1:0.1 to 1:2, said method comprising:

weighing cisplatin and the special carrier in a solvent, which is water, methanol, ethanol, acetone, 0.1% to 99% by volume methanol in water, 0.1 to 99% by volume acetone in water, 0.05% to 5.0% by weight sodium chloride in water, or 0.0001 to 1.0 N hydrochloric acid, or a mixture thereof, to form an aliquot so that the percentage of cisplatin is 0.005% to 0.25% by weight in the aliquot,

stirring the aliquot overnight or until it becomes a solution,

filtering through a filter with a porosity of between 0.1 .mu.m, and

drying the filtrate.

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L16: Entry 13 of 28

File: USPT

Dec 14, 1999

US-PAT-NO: 6001817

DOCUMENT-IDENTIFIER: US 6001817 A

TITLE: Pharmaceutical composition comprised of cisplatin, and processes for making and using same

DATE-ISSUED: December 14, 1999

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------|-----------|-------|----------|---------|
| Shaw; Jiajiu | Ann Arbor | MI | | |

ASSIGNEE-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY | TYPE CODE |
|-------------------------------|-----------|-------|----------|---------|-----------|
| Unitech Pharmaceuticals, Inc. | Ann Arbor | MI | | | 02 |

APPL-NO: 9/ 005523 [PALM]

DATE FILED: January 12, 1998

INT-CL: [6] A01 N 43/04

US-CL-ISSUED: 514/45; 514/46, 514/47, 514/48, 514/49, 514/50, 514/51, 514/19, 514/885, 536/26.7, 536/26.8, 536/27.6, 536/27.81, 536/28.5, 536/28.53, 536/28.54
US-CL-CURRENT: 514/45; 514/19, 514/46, 514/47, 514/48, 514/49, 514/50, 514/51, 514/885, 536/26.7, 536/26.8, 536/27.6, 536/27.81, 536/28.5, 536/28.53, 536/28.54

FIELD-OF-SEARCH: 514/45, 514/46, 514/47, 514/49, 514/50, 514/51, 514/19, 536/26.7, 536/26.8, 536/27.6, 536/27.81, 536/28.5, 536/28.53, 536/28.54

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

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| | PAT-NO | ISSUE-DATE | PATENTEE-NAME | US-CL |
|--------------------------|----------------|---------------|-----------------|-------|
| <input type="checkbox"/> | <u>4207416</u> | June 1980 | Hoeschele | |
| <input type="checkbox"/> | <u>5466678</u> | November 1995 | Kawabata et al. | |
| <input type="checkbox"/> | <u>5529775</u> | June 1996 | Mikulski et al. | |

OTHER PUBLICATIONS

Hollis et al., J. Med Chem., vol. 32, No. 1, pp. 128-136 (1989).
Peresie et al., Inorganica Chimica Acta, vol. 29, pp. L247-L248, (1978).

ART-UNIT: 163

PRIMARY-EXAMINER: Wilson; James O.

ATTY-AGENT-FIRM: Brinks Hofer Gilson & Lione

ABSTRACT:

A pharmaceutical composition, comprising cisplatin, a special carrier and, optionally, customary pharmaceutical excipients, is disclosed. The preparation of this pharmaceutical composition is also disclosed. The composition may be used to treat cancer and Acquired Immune Deficiency Syndrome (AIDS).

6 Claims, 0 Drawing figures